CLAIMS

What is claimed is:

1. A method of assessing relative susceptibility of a human to an undesirable bone density condition, the method comprising assessing occurrence in the human's genome of at least two disorder-associated polymorphisms in one or more genes selected from the group consisting of

a) genes which encode a protein component of bone matrix;

b) genes which encode an enzyme that catalyzes synthesis of an organic component of bone matrix;

c) genes which encode an enzyme that catalyzes deconstruction of an organic component of bone matrix;

d) genes which encode a protein that facilitates mineralization of bone matrix;

e) genes which encode a protein that facilitates de-mineralization of bone matrix;

f) genes which encode a protein that influences, by way of a transmembrane signaling pathway of a bone cell, expression of a protein selected from the group consisting of

i) a component of bone matrix;

ii) an enzyme that catalyzes synthesis of an organic component of bone matrix;

iii) an enzyme that catalyzes deconstruction of an organic component of bone matrix;

iv) a protein that facilitates mineralization of bone matrix; and

v) a protein that facilitates de-mineralization of bone matrix;

g) genes which encode a protein associated with vitamin D uptake or with vitamin D metabolism;

h) genes which encode a protein for which the level of expression of the protein is associated with bone erosion;

i) genes which encode a protein for which the level of expression of the protein is associated with bone resorption; and

j) genes which encode a protein for which the level of expression of the protein is associated with bone formation,

whereby occurrence of any of the polymorphisms is an indication that the human is more susceptible to an undesirable bone density condition than a human whose genome does not comprise the polymorphism, and whereby occurrence of a plurality of the polymorphisms is an indication that the human is even more susceptible to an undesirable bone density condition than a human whose genome does not comprise the polymorphisms.

2. The method of claim 1, wherein the genes are selected from the group consisting of a), b), c), d), e), f), and g).

3. The method of claim 1, wherein the genes are selected from the group consisting of a), b), c), d), and e).

4. The method of claim 1, wherein the genes are selected from the group consisting of f) and g).

5. The method of claim 1, further comprising assessing the occurrence in the genome of disorder-associated polymorphisms in at least one gene which encodes a component of a transmembrane signaling pathway of a bone cell.

6. The method of claim 5, wherein the bone cell is an osteoblast.

7. The method of claim 5, wherein the bone cell is an osteoclast.

8. The method of claim 1, wherein the genes are selected from the group consisting of

i) the gene which encodes parathyroid hormone (PtH);

ii) a gene which encodes a PtH receptor;

iii) the gene which encodes calcitonin;

iv) a gene which encodes a calcitonin receptor;

v) a gene which encodes a vitamin D receptor;

vi) the gene which encodes osteocalcin;

vii) the gene which encodes tumor necrosis factor-alpha 1;

viii) a gene which encodes a tumor necrosis factor-alpha 1 receptor;

ix) the gene which encodes transforming growth factor beta;

x) the gene which encodes the alpha 1 subunit of type 1 collagen;

xi) a gene which encodes an estrogen receptor;

xii) the gene which encodes interleukin-6;

xiii) a gene which encodes an interleukin-6 receptor;

xiv) the gene which encodes bone morphogenic protein;

xv) the gene which encodes apolipoprotein E;

xvi) the gene which encodes vitamin D 1 alpha-hydroxylase;

xvii) the gene which encodes insulin-like growth factor 1;

xviii) the gene which encodes the calcium sensing receptor of parathyroid gland cells; and

xix) the gene which encodes aromatase cytochrome P-450.

9. The method of claim 1, wherein the genes include a gene encoding one of a vitamin D receptor, transforming growth factor beta, an estrogen receptor, and interleukin-6.

10. The method of claim 1, wherein occurrence of the polymorphisms is assessed in at least three of the genes.

11. The method of claim 1, wherein occurrence of the polymorphisms is assessed in at least four of the genes.

12. The method of claim 1, wherein occurrence of the polymorphisms is assessed in at least six of the genes.

13. The method of claim 1, wherein occurrence of the polymorphisms is assessed in at least ten of the genes.

14. The method of claim 1, wherein occurrence of an individual disorder-associated polymorphism is assessed by

contacting a nucleic acid derived from the human's genome with a first oligonucleotide that anneals with higher stringency with the disorder-associated polymorphism than with a corresponding non-disorder-associated polymorphism and

assessing annealing of the first oligonucleotide and the nucleic acid,

whereby annealing of the first oligonucleotide and the nucleic acid is an indication that the human's genome comprises the disorder-associated polymorphism.

15. The method of claim 14, wherein the first oligonucleotide is attached to a support.

16. The method of claim 15, wherein the support has a plurality of different first oligonucleotides attached thereto.

17. The method of claim 16, wherein the support has attached thereto at least two first oligonucleotides that anneal with higher stringency with the disorder-associated polymorphisms than with the corresponding non-disorder-associated polymorphisms.

18. The method of claim 16, wherein the support has attached thereto at least four first oligonucleotides that anneal with higher stringency with the disorder-associated polymorphisms than with the corresponding non-disorder-associated polymorphisms.

19. The method of claim 16, wherein the support has attached thereto at least six first oligonucleotides that anneal with higher stringency with the disorder-associated polymorphisms than with the corresponding non-disorder-associated polymorphisms.

20. The method of claim 14, wherein the first oligonucleotide is a molecular beacon oligonucleotide.

21. The method of claim 14, wherein occurrence of an individual disorder-associated polymorphism is further assessed by

contacting the nucleic acid with a second oligonucleotide that anneals with higher stringency with a non-disorder-associated polymorphism than with the corresponding non-disorder-associated polymorphism and

assessing annealing of the second oligonucleotide and the nucleic acid,

whereby annealing of the second oligonucleotide and the nucleic acid is an indication that the human's genome does not comprise the disorder-associated polymorphism.

22. The method of claim 21, wherein the second oligonucleotide is attached to a support.

23. The method of claim 22, wherein the first and second oligonucleotides are attached to the same support.

24. The method of claim 21, wherein the second oligonucleotide is a molecular beacon oligonucleotide.

25. The method of claim 24, wherein the first and second oligonucleotides are spectrally distinct molecular beacon oligonucleotides.

26. The method of claim 1, further comprising calculating a susceptibility score by summing, for each of the selected genes in which a disorder-associated polymorphism occurs in the human's genome, the product of a constant and a correlation factor, wherein the correlation factor represents the fraction of humans heterozygous or homozygous for the disorder-associated polymorphism who exhibit the corresponding disorder, whereby the susceptibility score represents the relative susceptibility of the human to an undesirable bone density condition.

27. The method of claim 26, wherein the same constant is used for each selected gene.

28. The method of claim 27, wherein the constant used for each gene encoding one of a vitamin D receptor, transforming growth factor beta, interleukin-6, and an estrogen receptor is greater than the constant used for another selected gene.

29. The method of claim 28, wherein the constant used for each gene encoding one of a vitamin D receptor, transforming growth factor beta, interleukin-6, and an estrogen receptor is at least twice as great as the constant used for another selected gene.

30. The method of claim 1, wherein at least one of the polymorphisms is a single nucleotide polymorphism (SNP).

31. The method of claim 30, wherein occurrence of a SNP is assessed by annealing a nucleic acid derived from the human's genome with a primer that is complementary to the region adjacent the SNP on its 3' side, extending the primer using a polymerase in order to add a nucleotide residue complementary to the SNP to the primer, and detecting the identity of the nucleotide residue complementary to the SNP.

32. The method of claim 31, wherein the nucleotide residue is a non-extendable residue.

33. The method of claim 30, wherein the SNP is selected from the group consisting of

a) occurrence of a cytosine residue in the codon of the gene encoding transforming growth factor beta 1 protein corresponding to amino acid residue 10 of the protein, whereby the codon encodes proline;

b) occurrence of a thymine residue 8 residues upstream of the normal start codon of the gene encoding vitamin D receptor, whereby the residue is part of an initiation codon and the gene encodes a variant vitamin D receptor comprising three additional amino acids at its amino terminus;

c) occurrence of a nucleotide residue that is characteristic of apolipoprotein E polymorphic variant 4;

d) occurrence of a thymine residue in the gene encoding the alpha 1 subunit of type 1 collagen at a site at which a guanine residue normally occurs, whereby a recognition site for the transcription factor Sp1 is altered;

e) occurrence of a cytosine residue at position -174 of the interleukin 6 gene promoter;

f) occurrence of guanine residue at the position at which a cytosine residue normally occurs in the codon corresponding to amino acid residue 986 of the calcium sensing receptor gene, whereby the codon encodes a serine residue;

g) occurrence of a thymine residue at the position corresponding to position +1417 of the cDNA encoding a PtH receptor;

h) occurrence of a thymine residue at the position at which a cytosine residue normally occurs in the codon corresponding to amino acid residue 447 of the calcitonin receptor gene, whereby the codon encodes a leucine residue;

i) occurrence of a thymine residue at position +1377 of the calcitonin receptor gene; and

j) occurrence of a cytosine residue where a guanine residue normally occurs at the first nucleotide position of intron 2 of the PtH gene.

34. The method of claim 1, wherein at least one of the polymorphisms is occurrence of a thymine-adenine repeat at position -1174 upstream of exon 1 of the estrogen receptor gene.

35. The method of claim 1, wherein at least one of the polymorphisms is occurrence of a tetranucleotide simple tandem repeat in intron 4 of the aromatase cytochrome P-450 gene.

36. The method of claim 1, wherein at least one of the polymorphisms is occurrence of a cytosine-adenine repeat at a position from 947 to 984 residues upstream of the transcription start site of the insulin growth factor 1 gene.

37. A method of selecting a dose of a composition for administration to a human for modulating bone density in the human, the method comprising assessing occurrence in the human's genome of at least two disorder-associated polymorphisms in one or more genes selected from the group consisting of

a) genes which encode a protein component of bone matrix;

b) genes which encode an enzyme that catalyzes synthesis of an organic component of bone matrix;

c) genes which encode an enzyme that catalyzes deconstruction of an organic component of bone matrix;

d) genes which encode a protein that facilitates mineralization of bone matrix;

e) genes which encode a protein that facilitates de-mineralization of bone matrix;

f) genes which encode a protein that influences, by way of a transmembrane signaling pathway of a bone cell, expression of a protein selected from the group consisting of

i) a component of bone matrix;

ii) an enzyme that catalyzes synthesis of an organic component of bone matrix;

iii) an enzyme that catalyzes deconstruction of an organic component of bone matrix;

iv) a protein that facilitates mineralization of bone matrix; and

v) a protein that facilitates de-mineralization of bone matrix;

g) genes which encode a protein associated with vitamin D uptake or with vitamin D metabolism;

h) genes which encode a protein for which the level of expression of the protein is associated with bone erosion;

i) genes which encode a protein for which the level of expression of the protein is associated with bone resorption; and

j) genes which encode a protein for which the level of expression of the protein is associated with bone formation,

whereby occurrence of any of the polymorphisms is an indication that a greater dose of the composition should be administered to the human than to a human in whose genome the polymorphism does not occur; and

selecting a dose of the composition based on occurrence of the polymorphisms.

38. A kit for assessing relative susceptibility of a human to an undesirable bone density condition, the kit comprising reagents for assessing occurrence in the human's genome of at least two disorder-associated polymorphisms in one or more genes selected from the group consisting of

a) genes which encode a protein component of bone matrix;

b) genes which encode an enzyme that catalyzes synthesis of an organic component of bone matrix;

c) genes which encode an enzyme that catalyzes deconstruction of an organic component of bone matrix;

d) genes which encode a protein that facilitates mineralization of bone matrix;

e) genes which encode a protein that facilitates de-mineralization of bone matrix;

f) genes which encode a protein that influences, by way of a transmembrane signaling pathway of a bone cell, expression of a protein selected from the group consisting of

i) a component of bone matrix;

ii) an enzyme that catalyzes synthesis of an organic component of bone matrix;

iii) an enzyme that catalyzes deconstruction of an organic component of bone matrix;

iv) a protein that facilitates mineralization of bone matrix; and

v) a protein that facilitates de-mineralization of bone matrix;

g) genes which encode a protein associated with vitamin D uptake or with vitamin D metabolism;

h) genes which encode a protein for which the level of expression of the protein is associated with bone erosion;

i) genes which encode a protein for which the level of expression of the protein is associated with bone resorption; and

j) genes which encode a protein for which the level of expression of the protein is associated with bone formation.

39. The kit of claim 38, wherein the reagents comprise first oligonucleotides that anneal with higher stringency with the disorder-associated polymorphisms than with corresponding non-disorder-associated polymorphisms.

40. The kit of claim 39, wherein each of the first oligonucleotides is attached to a support.

41. The kit of claim 40, wherein each of the first oligonucleotides is attached to the same support.

42. The kit of claim 40, wherein each of the first oligonucleotides is attached to a different support.

43. The kit of claim 39, wherein the first oligonucleotides are molecular beacon oligonucleotides.

44. The kit of claim 39, wherein the kit further comprises second oligonucleotides that anneal with higher stringency with the non-disorder-associated polymorphisms than with corresponding disorder-associated polymorphisms.

45. The kit of claim 44, wherein the first and second oligonucleotides corresponding to the same polymorphism are a spectrally distinct molecular beacon oligonucleotide pair.

46. The kit of claim 38, wherein the reagents comprise primers that are complementary to the region adjacent a characteristic residue of the disorder-associated polymorphism for amplifying at least the characteristic residue.

47. The kit of claim 46, further comprising a polymerase capable of extending the primers by adding a nucleotide residue complementary to the characteristic residue.

48. The kit of claim 47, further comprising a non-extendable nucleotide residue.

49. The kit of claim 38, further comprising an instructional material which includes a numerical value representing the product of a constant and a correlation factor, wherein the correlation factor represents the fraction of humans heterozygous or homozygous for the disorder-associated polymorphism who exhibit the corresponding disorder.

50. The kit of claim 49, wherein the same constant is used for each selected gene.

51. The kit of claim 49, wherein the constant used for each gene encoding one of a vitamin D receptor, transforming growth factor beta, an estrogen receptor, and interleukin-6 is greater than the constant used for another selected gene.

52. The kit of claim 49, wherein the constant used for each gene encoding one of a vitamin D receptor, transforming growth factor beta, an estrogen receptor, and interleukin-6 is at least twice as great as the constant used for another selected gene.

53. The kit of claim 38, wherein the genes are selected from the group consisting of a), b), c), d), e), f), and g).

54. The kit of claim 38, wherein the genes are selected from the group consisting of a), b), c), d), and e).

55. The kit of claim 38, wherein the genes are selected from the group consisting of f) and g).

56. The kit of claim 38, wherein the genes are selected from the group consisting of

i) the gene which encodes parathyroid hormone (PtH);
ii) a gene which encodes a PtH receptor;
iii) the gene which encodes calcitonin;
iv) a gene which encodes a calcitonin receptor;
v) a gene which encodes a vitamin D receptor;
vi) the gene which encodes osteocalcin;
vii) the gene which encodes tumor necrosis factor-alpha 1;
viii) a gene which encodes a tumor necrosis factor-alpha 1 receptor;
ix) the gene which encodes transforming growth factor beta;
x) the gene which encodes the alpha 1 subunit of type 1 collagen;
xi) a gene which encodes an estrogen receptor;

xii) the gene which encodes interleukin-6;

xiii) a gene which encodes an interleukin-6 receptor;

xiv) the gene which encodes bone morphogenic protein;

xv) the gene which encodes apolipoprotein E;

xvi) the gene which encodes vitamin D 1 alpha-hydroxylase;

xvii) the gene which encodes insulin-like growth factor 1;

xviii) the gene which encodes the calcium sensing receptor of parathyroid gland cells; and

xix) the gene which encodes aromatase cytochrome P-450.